AD_____

Award Number: W81XWH-13-2-0021

TITLE: Basic Cognitive Neuroscience of Memory and Self-Appraisals in PTSD

PRINCIPAL INVESTIGATOR: Charles R. Marmar, MD

CONTRACTING ORGANIZATION: New York University
New York, NY 10016-6402

REPORT DATE: February 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
FEB 2014	Annual	15 JAN 2013-14 JAN 2014

4. TITLE AND SUBTITLE
Basic Cognitive Neuroscience of Memory and Self-Appraisals in PTSD

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-13-2-0021

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Charles R. Marmar, MD

E-Mail: Charles.Marmar@nyumc.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

New York University
New York, NY 10016-6402

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This proposal seeks to employ theories and paradigms from cognitive neuroscience to identify cognitive and neurobiological mechanisms underlying the relation between changes in self-efficacy (a core feature of self-identity) and combat-related PTSD. The discovery of such mechanisms will offer a novel means for conceptualizing PTSD, and will ultimately provide information that drives future research and therapeutic innovations informed directly by basic science, which in turn, may help to mitigate negative outcomes associated with PTSD.

15. SUBJECT TERMS
Self-efficacy: one's perceived capacity to manage stressful life events.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	10	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

INTRODUCTION:

Changes in self-identity are associated with a greater risk of PTSD,[1] poor treatment prognosis,[2] and suicidal ideation.[3] Combat appears to have a lasting impact on the identity of individuals deployed to war zones. This proposal seeks to employ theories and paradigms from cognitive neuroscience to identify cognitive and neurobiological mechanisms underlying the relation between changes in self-efficacy (a core feature of self-identity) and combat-related PTSD. The substantial number of individuals with PTSD that remain symptomatic post-treatment indicates the presence of pathological mechanisms that have yet to be examined or fully understood. Therefore, studies targeting the basic cognitive mechanisms and neurobiology of PTSD are a necessary first step in clarifying factors associated with risk in the onset and maintenance of PTSD. This study includes an analog and clinical phase (Phase 1 and Phase 2 respectively). In Phase 1, 120 healthy, civilian participants receive a self-efficacy induction, after which their affective responses to a trauma-film paradigm are monitored and their fear circuitry activation is examined using fMRI. Phase 2 consists of 4 experiments with 300 OEF/OIF veterans examining their self-efficacy, autobiographical remembering, future imagining, anticipatory fear and emotional expression using both behavioral and neuroimaging paradigms. These findings have the potential to deliver information that drives future research in therapeutic innovations and resilience training informed directly by basic science, which in turn, may help to mitigate negative outcomes associated with combat-related PTSD.

GOALS:

The major goals of this study are:

1. Test whether increasing perception of self-efficacy reduces maladaptive cognitive and affective responses following exposure to a trauma film video.

2. Examine the neural basis of affect regulation by increasing perceptions of self-efficacy during fMRI tasks among healthy control participants

3. Examine the cognitive processes and neural activation patters associated with memory and future thinking in PTSD

4. Examine the neural basis of affect regulation by increasing perceptions of self-efficacy during fMRI tasks among OEF/OIF veterans with and without PTSD

PROJECT ACCOMPLISHMENTS:

The Basic Cognitive Neuroscience of Self-Appraisals and Memory in PTSD study has completed the development phase and is now in the implementation phase. In Year 1 of the grant we accomplished several milestones and goals outlined in the Statement of Work. Our success in meeting these goals is detailed below.

1. **IRB**

We secured IRB approval from all regulatory sites including NYU School of Medicine and the DOD. In addition the IRB protocols underwent amendments to reflect new provisions:

Phase 1, Experiments 1 and 2: Eligible participants in Experiments 1 and 2 of Phase 1 are now asked to complete an online survey through the program Qualtrics Survey Software. Additionally, the online diary used in Experiment 1 of Phase 1 was replaced with a packet that participants can carry with them throughout the week.

Phase 2, Experiments 2-4: Multiple validated, minimal risk self-report measures have been added to the protocol in order to enrich the dataset and better assess participants' health status.

Eligibility Criteria: The inclusion and exclusion requirements of controls and veterans have been modified; they are listed in the protocol. We've modified the requirements to be consistent with the Steven and Alexandra Cohen Veterans Center for the Study for Post-Traumatic Stress Disorder and Traumatic Brain Injury recruitment protocol.

All subjects participating in an MRI scan are required to provide a urine sample for drug testing and pregnancy testing (when applicable). Women who are pregnant are not allowed to partake in the MRI scan as it may be dangerous for the fetus. We also want to confirm that participants do not test positive for drugs as that may affect the neuroimaging results. This requirement is reflected in the protocol and consent forms.

Informed Consent: Language used to describe the MRI scanning in both the consent form for controls and the consent form for veterans has been altered to comply with NYU's Center for Brain Imaging regulations. In addition, the consent forms for controls and veterans have been changed to specify that if participants are determined to be ineligible after their arrival to any of the MRI scanning sessions and thus do not complete the study, they will still be reimbursed $25.00 for their time. The consent form for veterans has also received a minor change- subjects that were recruited from previous studies conducted by the PTSD Research Program are given the option to release their clinical information from those studies to be used in the current one. This will decrease the burden on participants to provide duplicate information.

Recruitment: The recruitment of controls now includes NYU and Sarah Lawrence College. In addition, controls are no longer limited to undergraduate students and the age range has been extended from 20-40 to 20-60 years old. The recruitment of veterans has been changed to include subjects from the Steven and Alexandra Cohen Veterans Center for the Study for Post-Traumatic Stress Disorder and Traumatic Brain Injury who have previously consented to be contacted for future studies. When our protocol was initially submitted for IRB approval, the Steven and Alexandra Cohen Veterans Center for the Study for Post-Traumatic Stress Disorder and Traumatic Brain Injury had not been established. The addition of subjects recruited from the Cohen Center study will aid in the recruitment and testing of participants.

Minor changes have also been made to the advertisements to better reflect what the experiments entail and they have been made into separate documents to receive IRB stamp of approval so that they may be distributed to potential participants.

Personnel: The original PI, Dr. Adam Brown, was replaced with Dr. Charles Marmar. Dr. Adam Brown joined the faculty in the department of psychology at Sarah Lawrence College. He holds an adjunct assistant professorship at NYU School of Medicine, and continues to help oversee the project, but his new position no longer allows him to serve as a PI on grants at NYU.

Other: The MRI Subject Screening Form is now given to all participants that have consented to an MRI scan has been added because NYU's Center for Brain Imaging requires that all subjects complete it.

2. Personnel

The research team has been trained in all study procedures. In addition, the original PI, Dr. Adam Brown, was replaced with Dr. Charles Marmar. Dr. Adam Brown joined the faculty in the department of psychology at Sarah Lawrence College. He holds an adjunct assistant professorship at NYU School of Medicine, and continues to help oversee the project, but his new position no longer allows him to serve as a PI on grants at NYU. We have received IRB approval for this change.

The research team meets weekly to review the study's progress. Dr. Brown speaks with the staff on a daily basis. Consultants are contacted as needed and are updated regularly on the progress of the study.

3. Subject Recruitment, Enrollment and Completion

Healthy controls are currently being recruited and are participating in Experiments 1 and 2 of Phase 1. Veterans from the Biomarkers for PTSD study and the Steven and Alexandra Cohen Veterans Center for the Study for Post-Traumatic Stress Disorder and Traumatic Brain Injury are currently being recruited for Phase 2. We are running Experiment 1 of Phase 2 and preparing to implement Experiment 2 of Phase 2 in March 2014. The table below details current subject accrual data:

Table 1. Subject Recruitment, Enrollment and Completion Data

Experiment	Recruited Subjects	Screened Subjects	Eligible Subjects	Ineligible Subjects	Enrolled Subjects	Completed Subjects
Phase 1, Exp. 1	90	58	42	16	26	18
Phase 1, Exp. 2	137	48	33	15	18	17
Total non-clinical	**227**					**35**

Phase 2, Exp. 1	51				51	48
Phase 2, Exp. 2	12					0
Phase 2, Exp. 3						0
Phase 2, Exp. 4	12					0
Total clinical	**51**					**48**
Total						**83**

4. Database Construction and Tracking

A secure database has been developed. All clinical assessment data from the self-report and neurocognitive measures for all participants in Experiments 1 and 2 of Phase 1 and Experiment 1 of Phase 2 has been completed cleaned and entered as digital data directly into the study secure database server. Additionally, all neuroimaging data for all participants in Experiment 2 of Phase 1 has been transferred to the study secure database server and is being analyzed using the FSL neuroimaging software.

5. Acquisition of Study procedures

Study procedures used in Experiments 1 and 2 of Phase 1 including MRI imaging, and Experiment 1 of Phase 2 are completely operational.

6. Standard Operating Procedure (SOP) Manuals

SOPs have been developed for Experiments 1 and 2 of Phase 1, and Experiments 1-4 of Phase 2.

7. Preliminary Analysis

Phase 1, Experiment 1: Currently 18 healthy volunteers have completed this experiment. Participants were randomly assigned to the High Self-Efficacy condition (N = 8), the Low Self-Efficacy condition (N = 7) and the Neutral Self-Efficacy condition (N = 3). The data has been entered into the study secure database server but has not been analyzed due to the fact that the subject pool is currently underpowered to report any group differences.

Phase 1, Experiment 2: Analysis of neuroimaging data for 11 subjects has begun, and we have established that we are getting results that suggest that the paradigm is working and that we are successfully acquiring neuroimaging data. The experimental task exposes participants to time intervals when they may receive mild electrical shocks, and other intervals when they know they will not receive any shocks. Analysis of neuroimaging

data shows robust group-level activation in visual cortex in response to changing visual stimuli. Additional group means of interest include significant levels of deactivation in ventromedial PFC during the shock-related intervals. (This deactivation is also significantly lower than that seen in the non-shock-related trials) We have also begun to examine the effects of our self-efficacy induction on brain activity, but as yet have only six and five subjects in each group, and thus no significant differences to report.

Phase 2, Experiment 1: OEF/OIF veterans were randomized to either a High Self Efficacy or Control condition. In the High Self Efficacy condition, individuals were asked to recall three autobiographical memories associated with success and self-efficacy. In the Control condition, participants recalled any three personally significant memories. After this task, participants completed a social problem-solving task. Specifically, participants listened to two military-related vignettes in which a protagonist is confronted with a specific problem or issue to be resolved. Based on the scoring system of the Means End Problem Solving Task (MEPS, Platt & Spivack, 1975) quantitative scores were computed for relevant means (discrete steps that enable the protagonist to move closer to the goal). In addition, qualitative scoring was also used to identify the subject's overall effectiveness, as well as the degree to which they statements incorporated agency-related content. Consistent with the hypothesis stated in the grant, preliminary analyses reveal that OEF/OIF individuals in the High Self-Efficacy condition preformed better on these three indices of social problem solving task (see results presented in Table 2).

Table 2. Performance on the MEPS by High Self Efficacy or Control condition

	High Self Efficacy Condition	Control Condition
Variable	*M*	*M*
MEPS - Mean	5.62 (2.58)	4.37 (1.61)**
MEPS - Effectiveness	3.46 (0.93)	3.08 (0.88)*
MEPS - Active Statements	3.83 (0.81)	3.46 (0.98)*

MEPS = Means End Problem Solving Task. Mean = Number of solutions generated to solve problem. Effectives = Rating of overall quality of solutions generated for each strategy. Active Statements = Number of statements reflecting agency. **p < .05. *p < .15

OEF/OIF veterans in the High Self-Efficacy and Control condition were also asked to complete a Future Thinking Task. Participants were given 3 positive and 3 negative cue words and were asked to generate personally relevant imagined future events. Consistent with the hypothesis of this grant, OEF/OIF veterans in the High Self-Efficacy condition generated future events that reflect adaptive coping. For example, the future narratives generated by OEF/OIF individuals in the High Self Efficacy condition included a greater degree of agency-related statements, rated the future with a more positive outlook, and reported positive future events to be more "central to their self-identity". Such findings suggest that selectively recalling self-efficacious memories promotes adaptive future thinking in OEF/OIF veterans.

Table 3. Performance on the Future Thinking Task by High Self Efficacy or Control condition

	High Self Efficacy Condition	Control Condition
Variable	*M*	*M*
Future Thinking – Agency	4.00 (.68)	3.59 (.95)*
Future Thinking – Positive Valence	4.00 (0.42)	3.7 (0.51)**
Future Thinking– Positive Centrality Statements	4.49 (0.61)	4.15 (0.92)*

**p = .05. *p < .15

KEY RESEARCH ACCOMPLISHMENTS:

- Obtained IRB approvals across all sites and the DOD.
- Enrolled 28 healthy volunteers and 11 OIF/OEF veterans.
- Completed study procedures for 21 healthy volunteers and 47 OIF/OEF veterans.
- Research team participated in weekly study meetings.
- Entered, cleaned, and scored all data into a centralized database and ran reports for data analysis.
- Prepared preliminary analysis on a sample size of 47 OIF/OEF veterans.

CONCLUSION:

According to the Statement of Work, the tasks of months 1-12 of this study include:

1. Secure IRB approval from all regulatory sites (1-6 months)
2. Identify and Recruit Subjects (1-6 months)
3. Database Construction and Tracking (1-3 months)
4. Hire and Train Personnel (1-3 months)
5. Administer Analog Experiment 1 (months 6-12)
   The following tasks extend past year 1:
6. Administer Analog Experiment 2 (months 8-14)
7. Administer Clinical Experiment 1 (months 10-16)

In year 1 of the project we completed tasks 1, 2, 3 and 4. We are currently administering Phase 1, Experiments 1 and 2 and Phase 2, Experiments 1 and 2.

REFERENCES:

1. Ehlers A, Maercker A, Boos A. Post-traumatic stress disorder following political imprisonment: The role of mental defeat, alienation, and perceived permanent change. J Abnorm Psychol. 2000; 109: 45–55.

2. Ehlers A, Clark DM, Dunmore E, Jaycox L, Meadows E, Foa EB. Predicting response to exposure treatment in PTSD: The role of mental defeat and alienation. J Trauma Stress. 1998; 11: 457–471.

3. Brewin CR, Garnett R, Andrews B. Trauma, identity and mental health in UK military veterans. Psychol Med. 2010; 14:1-8.

4. Benight CC, Bandura A. Social cognitive theory of posttraumatic recovery: The role of perceived self-efficacy. Behaviour Research and Therapy. 2004; 42: 1129-1148.